

more fully clarify the invention. No new matter has been added by the amendments above. Favorable reconsideration is respectfully requested in light of the above amendments and the following comments.

The Examiner rejected claims 1-41, 44, 45, 53, and 54 under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse this rejection.

The Examiner rejected claims 1-8, 10-20, 23-38, 40, 41, 42, 44, and 45 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,273,900 (Boyce). Applicants respectfully traverse this rejection.

The Examiner rejected claims 9, 43, 53, and 54 under 35 U.S.C. § 102(b) as being anticipated by WO 91/16010 (Eisenberg). Applicants respectfully traverse this rejection.

The Examiner rejected claim 39 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,273,900 as applied to claim 20, and further in view of WO 91/16010. Applicants respectfully traverse this rejection.

### 35 U.S.C. § 112 Rejection

The Examiner rejected claims 1-41, 44, 45, 53, and 54 under 35 U.S.C. § 112, second paragraph. Favorable reconsideration is respectfully requested in light of the above amendments and the following comments.

The Examiner asserts that claims 1, 9, 12, 13, 20, and 21 are indefinite based on the limitation "essentially compact collagen membrane", because it is unclear what properties of the membrane are described by this term. This rejection has been addressed by the addition of the phrase "prepared by a compression of a collagen sponge at a pressure of at least about 50 bar". This renders the phrase "essentially compact collagen membrane" definite because the process by which they are formed is definite.

The Examiner asserts that claim 2 is indefinite because of the limitation "fluid selected from air and gaseous fluid". Claim 2 has been amended to render claim 2 more clear in the fluids that can be utilized.

The Examiner asserts that claim 2, 3, 4, 9, and 25 are indefinite because of the improper expression of alternative limitations. These claims have been amended to make the language more clearly comply with Markush claim format.

The Examiner asserts that claims 6, 7, 36 and 37 are indefinite because of the limitation "cells are originating substantially exclusively from". These claims have been amended to render the claims more clear.

The Examiner asserts that claims 8 and 38 recite the broad recitation of blood cells and also recite the limitation of "particularly macrophages or lymphocytes". The specific limitation in these claims has been removed, and placed into newly added claims 59 and 60 which are dependent on claims 8 and 38 respectively.

The Examiner asserts that claims 16, 19, 28, and 34 recite the limitation "one of the two layers", for which there is insufficient antecedent basis. This has been made more clear by the amendments made above.

The Examiner asserts that claim 20 is indefinite because it does not contain active method steps. Claim 20 has been amended to make it more clear what the active method steps are.

The Examiner asserts that claim 34 is indefinite because of the limitation "concomitant culture". Applicants believe that the Examiner is referring to claim 41 in which the above phrase is contained. Consequently, claim 41 has been amended to render the claim more clear.

In light of the above amendments and remarks, Applicants respectfully request favorable reconsideration in the form of a withdrawal of this rejection.

### 35 U.S.C. § 102 Rejections

The Examiner rejected claims 1-8, 10-20, 23-38, 40, 41, 42, 44, and 45 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,273,900 (Boyce). Although this rejection has not been raised with respect to the newly amended claims, it will be addressed to the extent that it may be applied.

The Examiner asserts that Boyce teaches a composite skin replacement comprising two components: an epidermal component and a porous, laminated dermal membrane. The dermal membrane is prepared from bovine collagen and a glycosaminoglycan, a polysaccharide. The membrane is covered with a laminating layer containing a mixture of collagen and glycosaminoglycan. The dermal membrane is then covered with normal keratinocytes.

The product of Boyce includes a dermal membrane that is covered with normal keratinocytes. The dermal membrane is prepared by freeze drying a second collagen gel on a first sponge which is also made by freeze drying.

Claim 1 has been amended to more fully describe the product of the invention. The invention includes a porous layer that is covered with a collagen membrane that can be an essentially compact collagen sponge. The essentially compact collagen sponge is prepared by compression of a collagen sponge at a pressure of at least about 50 bars. Formation of a sponge using compression at least about 50 bars gives a resulting sponge that is different than that of Boyce. Specifically, the essentially compact collagen sponge can be dense enough to impede the surface deposited keratinocytes from migrating downward into the subdermal sponge.

Because Boyce does not have a product that contains an essentially compact collagen sponge, Applicants assert that the disclosure of Boyce does not anticipate the Applicants' invention. Therefore Applicants respectfully request withdrawal of this rejection.

The Examiner rejected claims 9, 43, 53, and 54 under 35 U.S.C. § 102(b) as being anticipated by WO 91/16010 (Eisenberg). Although this rejection has not been raised with respect to the newly amended claims, it will be addressed to the extent that it may be applied.

The Examiner asserts that Eisenberg teaches a composite skin equivalent comprising a porous cross-linked sponge matrix comprising living fibroblasts and a layer of non-porous collagen, containing on its surface cultured keratinocyte cells.

As stated above, claim 1 has been amended to more fully describe the product of the invention. The invention includes a porous layer that is covered with a collagen membrane that can be an essentially compact a collagen sponge. The essentially compact collagen sponge is prepared by compression of a collagen sponge at a pressure of at least about 50 bars. Formation of a sponge using compression at least about 50 bars gives a resulting sponge that is different than that of Eisenberg. Specifically, the essentially compact collagen sponge can be dense enough to impede the surface deposited keratinocytes from migrating downward into the subdermal sponge.

The product of Eisenberg does not contain a compressed collagen sponge, and therefore Applicants assert that the disclosure of Eisenberg does not anticipate the Applicants' invention. Therefore, Applicants respectfully request withdrawal of this rejection.

### 35 U.S.C. § 103 Rejection

The Examiner rejected claim 39 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,273,900 as applied to claim 20, and further in view of WO 91/16010. Although this

rejection has not been raised with respect to the newly amended claims, it will be addressed to the extent that it may be applied.

In order to establish *prima facie* obviousness, three basic criteria must be met, namely: (1) there must be some suggestion or motivation to combine the references or modify the reference teaching; (2) there must be a reasonable expectation of success; and (3) the reference or references when combined must teach or suggest each claim limitation. Applicants submit that the Office Action failed to state a *prima facie* case of obviousness, and therefore the burden has not properly shifted to Applicants to present evidence of nonobviousness.

Applicants assert that the Examiner has failed to state a *prima facie* case of obviousness because the reference, or references fail to teach or suggest each claim limitation. As discussed above, neither of the references teach a compressed collagen sponge. Furthermore, neither of the references would suggest the use of a compressed collagen sponge because the migration that is allowed to occur in the sponges of Boyce and Eisenberg is not seen as a disadvantage.

Applicants also assert that the Examiner has failed to establish a *prima facie* case of obviousness because there is no motivation to modify the teachings of Boyce or combine the teachings of Eisenberg with Boyce. Based on the above, Applicants respectfully request withdrawal of this rejection.

### Conclusion

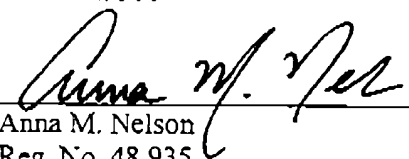
In view of the amendments and comments presented herein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested.

Respectfully submitted,

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Marked up version of Claims

1. (Amended) A composite acellular product forming a collagen support comprising at least one porous collagen layer covered on at least one side with an essentially compact collagen membrane selected from the group consisting of a collagen film prepared by drying a collagen gel and from a compressed collagen sponge prepared by a compression of a collagen sponge at a pressure of at least about 50 bar.
2. (Amended) The product according to claim 1 wherein said collagen gel is dried in a fluid selected from the group consisting of [from] air and [a gaseous fluid] gas.
3. (Amended) The product of claim 1, wherein the collagen of at least one of the porous layer and of the essentially compact membrane is selected from the group consisting of collagen and a mixture of collagen with a substance selected from [a] the group consisting of a polysaccharide, [,]a cellulose, dextran, an alginate and a carrageenan.
4. (Amended) The product of claim 3 wherein said polysaccharide is selected from the group consisting of glycosaminoglycan and chitosan.
5. (Amended) A composite product comprising the composite acellular product of claim 1, [and] wherein at least one of the porous layer and of the essentially compact membrane, comprises living cells selected from the group consisting of normal living cells, genetically modified living cells and malignant living cells.
6. (Amended) The product of claim 5, wherein said living cells [are] originat[ing]e substantially exclusively from young subjects.
7. (Amended) The product of claim 5, wherein said living cells [are] originat[ing]e substantially exclusively from elderly subjects.

8. (Amended) The product of claim 5, wherein the living cells are selected from the group consisting of fibroblasts, keratinocytes, melanocytes, Langerhans' cells originating from the blood, endothelial cells originating from the blood, blood cells, [particularly macrophages or lymphocytes,] adipocytes, sebocytes, chondrocytes, osteocytes, osteoblasts and Merkel's cells originating from the blood, said cells being normal, genetically modified or malignant.

9. (Amended) A composite product forming a collagen support comprising at least one porous collagen layer covered on at least one side with an essentially compact collagen membrane selected from the group consisting of a collagen film prepared by drying a collagen gel and [from] a compressed collagen sponge prepared by a compression of a collagen sponge at a pressure of at least about 50 bar, said porous layer comprising living fibroblasts and said essentially compact membrane comprising on the surface thereof living cells selected from the group consisting of keratinocytes, melanocytes, Merkel's cells originating from the blood, Langerhans' cells originating from the blood, sebocytes, cells originating from the blood, and nerve cells, the surface layer containing the living cells being cultivated while caused to emerge at the air-liquid interface of a compatible culture medium, while the porous layer containing the fibroblasts remains immersed during said cultivation step to give a reconstructed skin composed of a reconstructed dermis, comprising the fibroblasts having colonized the porous collagen layer forming a three dimensional matrix, said dermis being covered with a multilayer epidermis comprising said collagen membrane.

10. (Amended) The product of claim 1, wherein the collagen sponge is compressed at a pressure of at least about 50 bar, [equivalent to about  $50 \cdot 10^5$  Pa, this compression optionally taking place at] and a temperature [ranging] between about 20°C and 80°C.

11. (Amended) The product of claim 10, wherein the pressure [ranges] is between about 50 bar [( $50 \cdot 10^5$  Pa)] and 200 bar [( $200 \cdot 10^5$  Pa), this compression optionally taking place] and at a temperature [ranging] between about 40°C and 60°C.

12. The product of claim 1, wherein the essentially compact membrane is prepared prior to combination with the porous layer.

13. (Amended) The product of claim 12, wherein after having prepared the membrane, [the] a collagen gel is deposited on at least one surface of the membrane and the combination of the collagen gel with the membrane is frozen and lyophilised to give said composite product.

16. (Amended) The product of claim 1, wherein at least one of the [two] porous layer and membrane layer[s] is produced from a collagen gel containing a mixture of soluble collagen and insoluble collagen.

17. (Amended) The product of claim 16, wherein said insoluble collagen comprises collagen fibers.

19. (Amended) The product of claim 1, wherein at least one of the [two] porous layer and compact layer[s] is produced from a collagen gel containing a mixture of soluble collagen and insoluble collagen, wherein the collagen is selected from the group consisting of type I collagen and type III collagen.

20. (Amended) A process for the manufacture of a composite product comprising at least one porous collagen layer covered on at least one side with an essentially compact collagen membrane, [wherein] comprising the steps of:

a) preparing the essentially compact collagen membrane [is prepared] either by drying a first collagen gel, or by compressing a collagen sponge, obtained by the freezing-lyophilization of a collagen gel at a pressure of at least 50 bar;

b) preparing separately a second collagen gel [is prepared separately];

c) depositing either the essentially compact membrane [is deposited] on the second collagen gel, or pouring the second collagen gel [is poured] onto the essentially compact membrane; and [finally]

d) freezing-lyophilizing the whole [is frozen-lyophilized] to give said composite product.

22. (Amended) The process of claim 20, wherein the collagen sponge is compressed at a pressure [ranging] between about 50 bar [(50.10<sup>5</sup> Pa)] and about 200 bar [(200.10<sup>5</sup> Pa)].

23. (Amended) The process of claim 20, wherein the compression step takes place at a temperature of between about 20°C and 80°C.

24. (Amended) The process of claim 20, wherein the collagen is selected from the group consisting of collagen and a mixture of collage with a substance selected from the group consisting of a polysaccharide, cellulose, dextran, an alginate and a carrageenan.

25. (Amended) The process of claim 24, wherein the polysaccharide is selected from the group consisting of a glycosaminoglycan and chitosan.

26. (Amended) The process of claim 20, wherein said collagen comprises [or is essentially consisting of] mammalian collagen.

27. (Amended) The process of claim 20, wherein said collagen comprises [or is essentially consisting of] bovine collagen.

28. (Amended) The process of claim 20, wherein at least one of the [two] porous layer and membrane layer[s], are crosslinked.

34. (Amended) The process of claim 20, wherein living cells are introduced into at least one of the [two] porous layer or membrane layer[s].

36. (Amended) The process of claim 34, wherein said living cells [arc] originat[ing]e substantially exclusively from young subjects.

37. (Amended) The process of claim 34, wherein said living cells [are] originat[ing]e substantially exclusively from elderly subjects.



38. (Amended) The process of claim 34, wherein said living cells are selected from the group consisting of fibroblasts, keratinocytes, melanocytes, Langerhans' cells originating from the blood, endothelial cells originating from the blood, blood cells, [particularly macrophages or lymphocytes,] chondrocytes, osteocytes, [particularly] osteoblasts, Merkel's cells originating from the blood, sebocytes, adipocytes and nerve cells.

40. (Amended) The process of claim 20, wherein living cells are deposited on the surface of the [compact] membrane, said cells being selected from the group consisting of keratinocytes, melanocytes, Merkel's cells originating from the blood, Langerhans' cells originating from the blood, sebocytes, cells originating from the blood, and nerve cells.

41. (Amended) The process of claim 34, wherein the living cells are provided either by the sequential culture or by the [concomitant] simultaneous culture of the different types of cells, these cells originating from culture or biopsy.

44. (Amended) The artificial skin of claim 42, wherein said artificial skin compris[ing]es living cells obtained substantially exclusively from young cells from young subjects.

45. (Amended) The artificial skin of claim 42, wherein said artificial skin compris[ing]es living cells obtained substantially exclusively from aged cells from elderly subjects.

53. (Amended) The artificial skin of claim 43, wherein said artificial skin comprises living cells obtained substantially exclusively from young cells originat[ed]ing from young subjects.

54. (Amended) The artificial skin of claim 43, wherein said artificial skin comprises living cells obtained substantially exclusively from aged cells originat[ed]ing from elderly subjects.

55. (Amended) A method of in vitro testing of the efficacy of a potential active substance comprising and using an artificial skin comprising living cells prepared substantially

exclusively from young cells taken from young subjects, said artificial skin being prepared essentially from a composite product as defined in claim 1.

56. (Amended) A method of in vitro testing of the efficacy of a potential active substance comprising [and] using an artificial skin comprising living cells prepared substantially exclusively from aged cells taken from elderly subjects, said artificial skin being prepared essentially from a composite product as defined in claim 1.

57. (Amended) A method of in vitro testing of the efficacy of a potential active substance comprising [and] using an artificial skin comprising living cells prepared substantially exclusively from young cells taken from young subjects, said artificial skin being prepared essentially from a composite product as defined in claim 9.

58. (Amended) A method of in vitro testing of the efficacy of a potential active substance comprising [and] using an artificial skin comprising living cells prepared substantially exclusively from aged cells taken from elderly subjects, said artificial skin being prepared essentially from a composite product as defined in claim 9.

